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Drug provides better kidney transplant survival rates than current standard of care

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For the first time, an immunosuppressive agent has shown better organ survival in kidney transplant recipients than a calcineurin inhibitor, the current standard of care, according to a worldwide study led by UC San Francisco and Emory University investigators.

The study of the drug belatacept, which carries short-term risks that include an increased possibility for a certain cancer, appears in the Jan. 28, 2016, issue of the *New England Journal of Medicine*.

"Belatacept is potentially a transformational drug in kidney transplantation because unlike the currently used calcineurin inhibitor drugs cyclosporine and tacrolimus, it is not toxic to the kidney," said lead author Flavio Vincenti, MD, a UCSF Health kidney and pancreas transplant specialist. "In fact, it helps preserve the function of the kidney over the long term and is more effective in suppressing antibodies against the kidney, which are important causes of late graft loss."

Kidney transplant recipients need to take drugs to prevent their immune systems from rejecting their new organs, but the drugs themselves can cause problems. Long-term use of calcineurin inhibitors can damage the transplanted kidneys and lead to cardiovascular disease and diabetes.

Belatacept Inhibits Immune Response

A seven-year, multi-center study showed that kidney transplant

recipients taking belatacept, a drug the U.S. Food and Drug Administration approved in 2011, experienced a rate of mortality and graft loss significantly lower than patients taking a calcineurin inhibitor-based regimen. The risk of death or loss of the transplanted kidney after seven years was 12.7 percent for belatacept, compared to 21.7 percent for cyclosporine A.

The study, called BENEFIT (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial) and sponsored by Bristol-Myers Squibb, began in 2006, and FDA approval in 2011 was partly based on the first three years of results. Belatacept acts as a "co-stimulation blocker," inhibiting one of two signals T cells needed to trigger an immune response.

"While the best uses of belatacept still need additional definition, these results indicate that using belatacept as standard of care has the potential to improve long-term outcomes that matter to patients," said study author Christian Larsen, MD, DPhil, professor of surgery and dean of Emory University School of Medicine.

Post-transplant drugs can cost tens of thousands of dollars per year, and a belatacept-based regimen is more expensive than one based on calcineurin inhibitors. Many U.S. insurance companies now cover belatacept as medically necessary for kidney transplant patients.

Belatacept is given by infusion monthly at a doctor's office, in contrast to calcineurin inhibitors, which are taken in daily pills at home.

BENEFIT Trial Results

In the BENEFIT study, 666 kidney transplant patients were divided into three groups that received either a more intense belatacept-based regimen (B1), a less intense belatacept-based regimen (B2) or a

cyclosporine A-based regimen (CsA). The study followed 447 patients for all 84 months. All groups received additional drugs to inhibit graft rejection (basiliximab, mycophenolate mofetil and corticosteroids) in the weeks immediately after their transplants.

After 84 months, the Kaplan-Meier adjusted mortality rate was 9.2, 8.2 and 14.4 percent for the B1, B2 and CsA groups, respectively. For adjusted graft loss, the rate was 4.7, 5.4 and 9.8 percent. The rate for combined mortality and graft loss was 12.7 percent, 12.8 percent and 21.7 percent.

Immediately after transplant, belatacept-treated patients had a higher rate of acute rejection, a temporary flare up of the immune system against the donated kidney. The acute rejection rates were 24.4 percent in B1 and 18.3 percent in B2, compared with 11.4 percent in CsA. However, in most cases, acute rejection was successfully treated with drugs and did not lead to graft failure.

Patients taking belatacept showed slight improvements in kidney function (glomerular filtration rate) over time, in comparison with a decline in the CsA group, and comparable rates of serious adverse events (70.8, 68.6 and 76 percent). Viral and fungal infections were the most frequent serious adverse events.

Belatacept carries an FDA-mandated warning for an increased risk of developing post-transplant lymphoproliferative disorder (PTLD), a type of cancer where white blood cells grow out of control after an organ transplant. In the BENEFIT study, PTLD occurred in three patients in the B1 group, two in B2 and two in CsA.

The study authors note that the results of the BENEFIT study contrast with those from the companion BENEFIT-EXT study, in which patients received "extended criteria" kidneys from donors who were older than

60 or had chronic diseases. In the BENEFIT-EXT study, mortality and graft loss rates were similar between B1, B2 and CsA groups.

"We are still learning how best to use belatacept in immunosuppression regimens to balance its long-term benefits with greater safety and efficacy in the short term," said Vincenti, a professor of medicine. "At UCSF, we have launched a specialized clinic for patients treated with belatacept with the aim of applying precision medicine to transplant immunosuppression therapy - similar to what is happening in oncology - by using blood cell markers and molecular biomarkers to optimize the drug's use and safety."

Provided by University of California, San Francisco